Journal of Affective Disorders 339 (2023) 854–859

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Identifying the DSM-5 mixed features specifier in depressed patients: A comparison of measures

Mark Zimmerman *, Daniel Mackin

Department of Psychiatry and Human Behavior, Brown Medical School, South County Psychiatry, Providence, RI, United States

ARTICLE INFO

Keywords:
Depression
Bipolar disorder
Mixed features
DSM-5 mixed features specifier

ABSTRACT

Background: A commonly used measure to assess mixed features in depressed patients is the Young Mania Rating Scale (YMRS), which only partially aligns with the DSM-5 criteria. Different algorithms on the YMRS have been used to approximate the DSM-5 mixed features criteria. In the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we examined the agreement and validity of different approaches towards assessing the mixed features specifier.

Methods: Three hundred nine depressed psychiatric patients were interviewed with the Structured Clinical Interview for DSM-IV, the DSM-5 Mixed Features Specifier Interview (DMSI) and the YMRS. Seven definitions of mixed features were examined, two based on the DMSI and five from the YMRS.

Results: The prevalence of mixed features varied 8-fold amongst the 7 definitions. The level of agreement between the YMRS definitions and the DMSI was poor. For each definition, mixed features were significantly more common in patients with bipolar disorder than major depressive disorder. A family history of bipolar disorder was significantly associated with the DMSI assessment of mixed features but none of the YMRS approaches.

Limitations: The ratings on the measures were not independent of each other. The sample size was too small to compare the patients with bipolar I and bipolar II disorder.

Conclusions: While there was evidence of validity for both the DSM-5 and YMRS approaches towards identifying mixed features, the 2 approaches are not interchangeable. The algorithm on the YMRS used to classify patients has a significant impact on prevalence.

1. Introduction

The occurrence of features of mania in patients with depression has been recognized for more than a century (Kraepelin, 1921), and in the modern DSM era this co-occurrence has been designated as mixed episodes. During the past couple of decades, the clinical significance of the co-existence of manic/hypomanic symptoms during an episode of major depression has been the subject of increased research. In patients with bipolar depression, co-occurring manic symptoms have been associated with greater suicidality (Bauer et al., 2006; Goldberg et al., 2009; Judd et al., 2012; Swann et al., 2007), poorer longitudinal course (Dodd et al., 2010; Judd et al., 2012), increased risk of manic symptoms in patients prescribed antidepressants (Goldberg et al., 2007), greater number of depressive episodes (Masi et al., 2001), and an increased risk of rapid cycling (Goldberg et al., 2009). In patients with major depressive disorder (MDD), co-occurring manic symptoms have likewise been associated with an increased risk of suicidal behavior (Olgiati et al., 2006; Perugi et al., 2015), more depressive episodes (Smith et al., 2009), poorer response to treatment (Smith et al., 2009), more atypical features of depression (Benazzi, 2004; Perugi et al., 2015), a younger age of onset (Benazzi, 2004; Perugi et al., 2015; Sato et al., 2003), and an increased familial risk of bipolar disorder (Benazzi, 2004; Perugi et al., 2015; Sato et al., 2003). Treatment guidelines have cautioned against the use of antidepressants in depressed patients with mixed symptoms due to an increased likelihood of initiating the onset of mania, indicating that the accurate classification of mixed features is of significant clinical importance (Grunze et al., 2018; Stahl et al., 2017; Verdolini et al., 2018; Yatham et al., 2021).

DSM-5 offered a new definition for mixed features in depression (American Psychiatric Association, 2013). A depressive episode with mixed features required the presence of 3 or more of 7 symptoms of mania/hypomania (euphoric/expansive mood, inflated self-esteem/grandiosity, hypertalkative/pressured speech, flight of ideas/thought racing, increased energy/goal directed activity, activity with potential

* Corresponding author at: 1170 Pontiac Avenue, Cranston, RI 02920, United States.
E-mail address: mzimmerman@lifespan.org (M. Zimmerman).

https://doi.org/10.1016/j.jad.2023.07.102
Received 19 April 2023; Received in revised form 9 July 2023; Accepted 19 July 2023
Available online 23 July 2023

painful consequences, and decreased need for sleep). To be sure, the DSM-5 definition of the mixed features specifier of depressive episodes has not been without controversy (Koukopoulos and Sani, 2014; Koukopoulos et al., 2013; Malhi et al., 2015; Perugi et al., 2015). Only the manic symptoms considered to be non-overlapping mood elevation symptoms are used to define the DSM-5 specifier. Thus, irritability, agitation, and distractibility, which are considered hallmark features of the mixed state by some authors (Koukopoulos and Sani, 2014; Koukopoulos et al., 2013), were not included in the definition. Also, the minimum number of features required by DSM-5 to indicate the presence mixed features has been deemed to be too high (Kim et al., 2016; Perugi et al., 2015).

While there is considerable interest in the significance of mixed features in depressed patients, and controversy as to how to best define mixed features in depressed patients, it is surprising that little attention has been given to the development of rating scales assessing the DSM-5 criteria. Rather, measures that were developed prior to the publication of the DSM-5 mixed features specifier criteria have been used as proxies for the DSM-5 criteria.

There are several clinician-rated measures of the severity of manic symptoms. The content of these scales overlap thereby resulting in significant correlations between them (Vieta et al., 2008), though there are also meaningful differences that can result in different response rates in bipolar depressed patients with mixed features (Shansis et al., 2016). The most commonly used measure to assess manic symptoms is the Young Mania Rating Scale (YMRS) (Young et al., 1978). The YMRS contains 11 items, each rated according to 5 grades of severity. Four items are rated 0, 2, 4, 6 or 8, whereas the other 7 items are rated 0, 1, 2, 3 or 4. No time frame is specified for the rating of items. The YMRS fully assesses 4 of the 7 DSM-5 mixed features specifier and partially assesses 3 of the 7 features. Only 1 aspect of the risk-taking behavior criterion is assessed by the YMRS (increased sexual activity). Only half of the increased energy/goal-directed activity criterion is assessed (i.e., increased energy, but not increased goal-direct activity). Additionally, no single item assesses grandiosity; however, this symptom is a component of an item assessing thought content (hyperreligiousity, grandiosity, paranoid or referential ideas). Table 1 summarizes the relationship between the content of the DSM-5 mixed features criteria and the YMRS. It is noteworthy that studies have used different algorithms based on the YMRS to approximate the DSM-5 mixed features criteria (Table 2).

Existing symptom severity scales are lacking in several additional ways. This includes items being rated on an ordinal scale, making it unclear where a cutoff to indicate the presence vs. absence of symptoms should be placed. Furthermore, the rating of symptom severity and presence is often based on the past week. This creates significant fidelity issues when assessing for mixed features according to the DSM-5, which requires that the manic/hypomanic features be present for the majority of the depressive episode.

Table 1
Items of the DSM-5 mixed features specifier and Young Mania Rating Scale (YMRS).

DSM-5 mixed features specifier criteria	YMRS items
Elevated mood	Elevated mood (YMRS item 1)
Inflated self-esteem, grandiosity	Thought content (YMRS item 8)
Hypertalkative, pressured speech	Speech—rate and amount (YMRS item 6)
Flight of ideas, thought racing	Language—thought disorder (YMRS item 7)
Increased energy, goal directed activity	Increased motor activity, energy (YMRS item 2)
Excess involvement pleasurable activities	Sexual interest (YMRS item 3)
Decreased need for sleep	Sleep (YMRS item 4)
	Irritability (YMRS item 5)
	Disruptive-aggressive behavior (YMRS item 9)
	Appearance (YMRS item 10)
	Insight (YMRS item 11)

Table 2
Scoring algorithms used in different studies to identify mixed features based on the Young Mania Rating Scale.

Study	YMRS items included/ excluded in algorithm	Item scoring	Definition of mixed features
Mazza et al. (2012)	All 11 items	0 vs. 1+	3 or more items present
Mcintyre et al. (2015b)	Excluded items 5 and 11	0 vs. 1+	3 or more items present
Mcintyre et al. (2015a)	All 11 items	Sum of all 11 items	Total score ≥ 4
Miller et al. (2016)	Excluded items 5, 10, and 11	0 vs. 1+	3 or more items present
Tohen et al. (2014)	Excluded items 3, 5, 8, 9, 10	0 vs. 1+	3 or more items present

As part of the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project, we developed a semi-structured interview that determines the presence of the DSM-5 mixed features specifier according to the DSM-5 definition (requiring symptom presence for the majority of the depressive episode) as well as based on symptom presence during the past week. In the present study we examined the association between the DSM-5 mixed features specifier and the various YMRS algorithms that have been used as proxies for the DSM-5 specifier. We examined the level of agreement between the 2 methods of subtyping, and the variations of these methods, their respective associations with the distinction between bipolar disorder and MDD, and their association with a family history of bipolar disorder.

2. Methods

2.1. Setting and measures

Three hundred nine patients with current DSM-IV/DSM-5 MDD or bipolar disorder (current episode depressed) presenting for an intake evaluation at the Rhode Island Hospital Department of Psychiatry partial hospital program were interviewed by a trained diagnostic rater who administered a modified version of the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) supplemented with the DSM-5 Mixed Features Specifier Interview (DMSI) and the YMRS (Young et al., 1978). A family history of bipolar disorder was based on information provided by the patient. The interview followed the guide provided in the Family History Research Diagnostic Criteria (FH-RDC) (Endicott et al., 1978) for all first-degree family members.

Details regarding interviewer training and diagnostic reliability are available in other publications from the MIDAS project, which have documented high reliability in diagnosing mood disorders (Zimmerman, 2003; Zimmerman and Mattia, 1999). Of relevance to the present report, the inter-rater reliability of the DMSI was examined in 27 patients and the kappa coefficient of agreement in diagnosing the DSM-5 mixed features specifier was 1.0. The Rhode Island Hospital institutional review committee approved the research protocol, and all patients provided informed, written consent.

The DMSI assesses the 7 criteria of the DSM-5 mixed features specifier (elevated mood, inflated self-esteem, increased talkativeness, thought racing, increased energy or goal directed activity, increased activity with potentially painful consequences, decreased need for sleep). The DSM-5 specifier requires the presence of at least three of the mixed features for the majority of the depressive episode. The probes of the DMSI inquire about symptom presence and severity for the past week and also determine if the symptom is present for the majority of the depressive episode.

2.2. Data analyses

We computed the overall percentage agreement and kappa (*k*) coefficient to examine the absolute and chance corrected level of agreement between the DSM-5 mixed features subtyping and the YMRS proxies for the DSM-5 specifier. The absolute or overall level of agreement between 2 measures refers to the number of patients who are classified the same, either with or without mixed features, divided by the total sample size. Kappa represents the level of agreement beyond that accounted for by chance. Other statistics have been used to correct for chance agreement, (Spitznagel and Helzer, 1985) but kappa is the most frequently used. Based on each definition of mixed features we compared the prevalence of mixed features in patients with bipolar disorder and MDD. For the patients with MDD we compared the patients who did and did not meet the mixed features specifier on the family history of bipolar disorder.

As detailed in Table 2, we applied 5 different algorithms on the YMRS to classify patients as having or not having mixed features.

3. Results

3.1. Demographic characteristics

Demographic information was missing for 1 patient. The sample included 74 (23.9 %) men and 234 (75.7 %) women who ranged in age from 18 to 78 years (mean = 35.5, SD =13.6). Nearly one-fourth of the subjects were married (22.7 %, *n* = 70) and nearly half were single (45.3 %, *n* = 140). The remainder were divorced (13.6 %, *n* = 42), separated (4.5 %, n = 14), widowed (1.0 %, n = 3), or living with someone as if in a marital relationship (12.6 %, *n* = 39). Approximately one fifth graduated from a 4-year college (20.7 %, *n* = 64), and an additional 39 (12.6 %) completed graduate or professional school. The racial and ethnic composition of the sample was 69.3 % (*n* = 214) nonHispanic white, 7.1 % (*n* = 22) black, 14.6 % (*n* = 45) Hispanic, 1.6 % (*n* = 5) Asian, and 7.1 % other (n = 22). The majority of the patients were diagnosed with MDD (89.3 %, *n* = 276). Approximately twice as many patients were diagnosed with bipolar II (6.8 %, n = 21) than bipolar I (3.9 %, *n* = 12) disorder.

3.2. Prevalence of mixed features according to different definitions

The prevalence of mixed features varied widely amongst the 7 definitions (Table 3). The narrowest definition was the DSM-5 definition (4.5 %), which requires 3 or more criteria for the majority of the episode. The broadest definition, which required 3 or more symptoms on the 11-item YMRS (35.9 %), was 8-fold higher than the DSM-5 definition. When the 2 items assessing irritability and insight on the YMRS (i.e., items 5 and 11) were excluded from consideration, and to be diagnosed with mixed features still required 3 or more of the remaining 9 items to be rated positive, then the prevalence of mixed features was markedly reduced to 9.7 %. The additional exclusion of item 10 (appearance) had no further impact on the prevalence of mixed features in our sample. Reducing the YMRS to a 6-item scale further lowered the prevalence of mixed features to 7.4 %.

Table 3
Percentage of depressed patients classified as mixed according to different definitions (*n* = 309).

Mixed features definition	n	%
DSM-5 mixed features specifier—majority episode	14	4.5
DSM-5 mixed features specifier—past week	26	8.4
11-Item YMRS—≥3 items present	111	35.9
11-Item YMRS—total score ≥ 4	76	24.5
9-Item YMRS—≥3 items present	30	9.7
8-Item YMRS—≥3 items present	30	9.7
6-Item YMRS—≥3 items present	213	7.4

The time frame used to assess the DSM-5 criteria had an impact on the prevalence of the mixed features specifier. Nearly twice as many patients met the DSM-5 mixed features specifier criteria during the week before the assessment (8.4 %) compared to the majority of the episode criteria (4.5 %). The proportion of patients meeting the mixed features criteria on the 6-item YMRS was approximately the same as the proportion meeting the DSM-5 criteria for the past week (7.4 % vs. 8.4 %).

3.3. Level of agreement between different definitions of mixed features

The level of agreement between the YMRS definitions and the DSM-5 majority of episode definition was poor (mean kappa = 0.18) (Table 4). The agreement between the YMRS definitions and the DSM-5 past week definition was higher, though still low (mean kappa = 0.34). High agreement was found between the 2 different ways of scoring the 11-item YMRS, and between the different reduced item versions of the YMRS. However, only modest agreement was found between the complete 11-item YMRS and the reduced item versions of the scale.

3.4. Association between the definitions of the mixed features specifier and mood disorder diagnosis

We examined the validity of the different definitions of mixed features from 2 perspectives. First, we examined the prevalence of mixed features in patients with MDD and bipolar depression (Table 5). For illustrative purposed we included the breakdown between bipolar 1 and bipolar 2 disorder though we did not directly compare these 2 groups due to small sample size in both groups. For each definition, mixed features were significantly more common in patients with bipolar disorder. For the DSM-5-TR definition, the odds ratio was same when the time frame was the majority of the episode or the past week (3.67, 3.64). Of note, when the YMRS definition was narrowed and the prevalence of mixed features reduced, the odds ratios comparing patients with bipolar disorder and MDD increased. Based on the 11-item YMRS the odds ratio was <3, whereas a shortened 8 or 9-item version of the YMRS achieved an odds ratio above 5.5.

3.5. Mixed features and family history of bipolar disorder in patients with MDD

Second, we examined the family history of bipolar disorder, one of the most important predictors of the transition from an MDD diagnosis to a bipolar diagnosis, in patients with MDD (Table 6). The only significant difference was for the DSM-5 definition based on the past week time frame. The difference in family history of bipolar disorder in patients with and without mixed features was similar for the DSM-5 definition based on the majority of episode time frame, but the difference was not significant due to the smaller sample size of positive cases. A family history of bipolar disorder did not differ between patients who did and did not have mixed features based on the YMRS definitions.

4. Discussion

Mixed features in depressed patients have been defined in different ways (Benazzi, 2008; Perugi et al., 2015). Mixed features have been assessed with different instruments (Azorin et al., 2012; Grover and Adarsh, 2023; Miller et al., 2016; Perlis et al., 2014; Tohen et al., 2014; Zimmerman, 2017; Zimmerman et al., 2014). Even when the same instrument is used, there is variability in how mixed features are identified (Mcintyre et al., 2015b; Mineo et al., 2022; Tohen et al., 2014). This inconsistency in definition and assessment can, understandably, contribute to a clinician being “mixed up” about mixed features (Castle, 2014).

Most studies of the DSM-5 mixed features specifier have used proxy measures to assess the DSM-5 criteria. The results of the present study suggest that these proxy measures may be valid indicators of mixed

Table 4
Concordance amongst different approaches towards classifying DSM-5 mixed features.

	DMSI majority episode		DMSI past week		11-item YMRS ≥3 items present		11-item YMRS Total score ≥ 4		9-item YMRS ≥3 items present		8-item YMRS ≥3 items present	
	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement	kappa	% agreement
DMSI – majority of episode	–	–	–	–	–	–	–	–	–	–	–	–
DMSI – past week	0.52	94.2	–	–	–	–	–	–	–	–	–	–
11-Item YMRS—≥3 items present	0.13	76.7	0.26	78.6	–	–	–	–	–	–	–	–
11-Item YMRS—total score ≥ 4	0.10	66.7	0.15	67.3	0.74	88.7	–	–	–	–	–	–
9-Item YMRS—≥3 items present	0.23	89.6	0.45	90.9	0.50	85.1	0.32	73.8	–	–	–	–
8-Item YMRS—≥3 items present	0.23	89.6	0.45	90.9	0.50	85.1	0.32	73.8	1.00	100	–	–
6-Item YMRS—≥3 items present	0.23	91.3	0.40	91.3	0.40	82.8	0.25	71.5	0.86	97.7	0.86	97.7

DMSI indicates DSM-5 mixed features specifier interview; YMRS indicates Young Mania Rating Scale.

Table 5
Frequency of mixed features subtype based on different definitions in patients with major depressive disorder and bipolar disorder.

Mixed features definition	MDD (n = 276)		Bipolar 1 (n = 12)				Bipolar 2 (n = 21)				Bipolar 1 or 2 (*n* = 33)			
	n	%	n	%	OR	95 % CI	n	%	OR	95 % CI	n	%	OR	95 % CI
DMSI mixed features														
Majority of episode	10	3.6	2	16.7	**5.32**	**1.03–27.54**	2	9.5	2.80	0.57–13.70	4	12.1	**3.67**	**1.08–12.44**
Past week	19	6.9	2	16.7	2.71	0.55–13.24	5	23.8	**4.23**	**1.40–12.79**	7	21.2	**3.64**	**1.40–9.47**
Young Mania Rating Scale algorithm														
All 11 items, ≥3 items present	61	22.1	6	50.0	**3.53**	**1.10–11.32**	9	42.9	**2.64**	**1.06–6.57**	15	45.5	**2.94**	**1.40–6.17**
All 11 items, total ≥ 4	93	33.7	8	66.7	**3.94**	**1.16–13.41**	10	47.6	1.79	0.73–4.37	18	54.5	**2.36**	**1.14–4.90**
9 items, ≥3 items present	20	7.2	4	33.3	**6.40**	**1.77–23.10**	6	28.6	**5.12**	**1.79–14.64**	10	30.3	**5.57**	**2.33–13.29**
8 items, ≥3 items present	20	7.2	4	33.3	**6.40**	**1.77–23.10**	6	28.6	**5.12**	**1.79–14.64**	10	30.3	**5.57**	**2.33–13.29**
6 items, ≥3 items present	16	5.8	4	33.3	**8.13**	**2.21–29.88**	3	14.3	2.71	0.72–10.16	7	21.2	**4.38**	**1.68–11.60**

Bolded items indicate a signifcant difference with the MDD group.

Table 6
Family history of bipolar disorder in major depressive disorder patients with and without mixed features according to different definitions[a].

	Mixed features absent		Mixed features present		OR	95 % CI
	n	%	n	%		
DMSI mixed features						
Majority of episode	57	27.0	5	50.0	2.70	0.75–9.68
Past week	53	26.0	9	52.9	**3.21**	**–8.73**
Young Mania Rating Scale algorithm						
All 11 items, ≥3 items present	48	27.1	14	31.8	1.25	0.61–2.57
All 11 items, total ≥ 4	42	28.0	20	28.2	1.01	0.54–1.89
9 items, ≥3 items present	58	27.9	4	30.8	1.15	0.34–3.88
8 items, ≥3 items present	58	27.9	4	30.8	1.15	0.34–3.88
6 items, ≥3 items present	58	27.9	4	30.8	1.15	0.34–3.88

Bolded items indicate a significant difference between groups.
[a] Family history information was only collected for 221 of the 276 patients with major depressive disorder.

features, but they agree poorly with a measure designed to directly evaluate the DSM-5 mixed features criteria.

We examined 7 ways of identifying mixed features—2 based on the DSM-5 criteria for the mixed features specifier varying only in the time frame used to diagnose, and 5 based on the YMRS varying in the algorithm used identify mixed features. Across the span of these 7 definitions there was an 8-fold difference in prevalence rates. The level of agreement between the DSM-5 and YMRS definitions was poor. The highest level of agreement between the DSM-5 and YMRS definitions was between the past week scoring of the DMSI and the reduced item versions of the YMRS. However, the agreement between these classifications was still modest, despite prevalence estimates being similar, and only the DMSI past week scoring was associated with family history of bipolar disorder.

Several treatment guidelines have described the treatment implications of mixed features in depressed patients. Specifically, treatment guidelines have cautioned against using antidepressants in patients with mixed features and recommended the use of mood stabilizers (Grunze et al., 2018; Stahl et al., 2017; Verdolini et al., 2018; Yatham et al., 2021). The treatment implications of mixed features increase the importance of determining the most valid approach towards diagnosing mixed features because of the disparity in prevalence rates as a function of assessment methodology. A broad diagnostic approach increases the likelihood of false positive diagnoses thereby resulting in overtreatment with unneeded medications and consequent exposure to potential side effects and medical risk. A narrower diagnostic approach increases the likelihood of false negative diagnoses with subsequent underprescription of mood stabilizing medications, overprescription of antidepressants, and an increased risk of poor outcome and increased costs of care. The present study highlights the need for more research examining the impact of assessment methodology on the prevalence and validity of different measures and algorithms for evaluating mixed features.

The present study was conducted in a partial hospital program where illness severity, chronicity, diagnostic comorbidity, and prior treatment failure is generally greater than outpatient settings. This may, therefore, be a particularly appropriate setting to develop and study mixed features because their presence predicts need for higher level of care (Smith et al., 2009). Conversely, given that the study was conducted in a single setting, the extent to which the results are generalizable needs to be demonstrated. While the generalizability of any single site study is

limited, a strength of the study was that the patients were unselected with regards to meeting any inclusion or exclusion criteria outside of the presence of an episode of depression. In the MIDAS project, patients are not selected because they are prototypic, and thus more severe variants, of any diagnostic construct. Nonetheless, replication of the results in samples with different demographic characteristics is warranted. It will also be important to replicate these findings in an outpatient sample.

The ratings on the measures were not independent of each other. That is, the same rater completed the DMSI and the YMRS. It would be preferable to have independent interviewers complete the clinician rating scales though this was not practical in an integrated clinical research setting such as ours in which the interview is conducted primarily for clinical purposes and the use of the information for research is a secondary goal.

Almost all of the patients presenting for treatment were taking psychotropic medication at the time of the evaluation. As part of the research protocol, we did not record the patients' medication status. The prevalence of mixed features may have been underestimated if the symptoms were partially treated. However, we do not believe that this would have had a differential impact on various definitions examined.

Another limitation of the study was the insufficient sample size to compare the patients with bipolar I and bipolar II disorder. We therefore compared a combined bipolar disorder group to the patients with MDD.

In conclusion, while there was evidence of validity for both the DSM and YMRS approaches towards identifying mixed features, the 2 approaches are not interchangeable. The algorithm on the YMRS used to classify patients with mixed features has a significant impact on prevalence.

Role of funding source

None.

CRediT authorship contribution statement

Mark Zimmerman designed the study, wrote the first draft of the manuscript, and directed the data analysis. Daniel Mackin managed and analyzed the data and reviewed the draft of the manuscript and provided feedback to Dr. Zimmerman that was incorporated into the final submission.

Declaration of competing interest

None.

Acknowledgments

None.

References

American Psychiatric Association (Ed.), 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th; DSM-5 ed. American Psychiatric Association, Arlington, VA.
Azorin, J.M., Kaladjian, A., Adida, M., Fakra, E., Belzeaux, R., Hantouche, E., Lancrenon, S., 2012. Self-assessment and characteristics of mixed depression in the French national EPIDEP study. J. Affect. Disord. 143, 109–117.
Bauer, M.S., Wisniewski, S.R., Marangell, L.B., Chessick, C.A., Allen, M.H., Dennehy, E. B., Miklowitz, D.J., Thase, M.E., Sachs, G.S., 2006. Are antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J. Clin. Psychiatry 67, 48–55.
Benazzi, F., 2004. Intra-episode hypomanic symptoms during major depression and their correlates. Psychiatry Clin. Neurosci. 58, 289–294.
Benazzi, F., 2008. Reviewing the diagnostic validity and utility of mixed depression (depressive mixed states). Eur. Psychiatry. 23, 40–48.
Castle, D.J., 2014. Bipolar mixed states: still mixed up? Curr. Opin. Psychiatry. 27, 38–42.
Dodd, S., Kulkarni, J., Berk, L., Ng, F., Fitzgerald, P.B., De Castella, A.R., Filia, S., Filia, K., Montgomery, W., Kelin, K., Smith, M., Brnabic, A., Berk, M., 2010. A prospective study of the impact of subthreshold mixed states on the 24-month clinical outcomes of bipolar I disorder or schizoaffective disorder. J. Affect. Disord. 124, 22–28.
Endicott, J., Andreasen, N., Spitzer, R.L., 1978. Family History Research Diagnostic Criteria, 3rd edition. Biometrics Research, New York State Psychiatric Institute, New York.
First, M.B., Spitzer, R.L., Williams, J.B.W., Gibbon, M., 1997. Structured Clinical Interview for DSM-IV (SCID). American Psychiatric Association, Washington, D.C.
Goldberg, J., Perlis, R., Ghaemi, S., Calabrese, J., Bowden, C., Wisniewski, S., Miklowitz, D., Sachs, G., Thase, M., 2007. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am. J. Psychiatry 164, 1348–1355.
Goldberg, J.F., Perlis, R.H., Bowden, C.L., Thase, M.E., Miklowitz, D.J., Marangell, L.B., Calabrese, J.R., Nierenberg, A.A., Sachs, G.S., 2009. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am. J. Psychiatry 166, 173–181.
Grover, S., Adarsh, H., 2023. A comparative study of prevalence of mixed features in patients with unipolar and bipolar depression. Asian J. Psychiatr. 81, 103439.
Grunze, H., Vieta, E., Goodwin, G.M., Bowden, C., Licht, R.W., Azorin, J.M., Yatham, L., Mosolov, S., Moller, H.J., Kasper, S., Members of The, W.F.S.B.P, 2018. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. World J. Biol. Psychiatry. 19, 2–58.
Judd, L.L., Schettler, P.J., Akiskal, H., Coryell, W., Fawcett, J., Fiedorowicz, J.G., Solomon, D.A., Keller, M.B., 2012. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J. Affect. Disord. 138, 440–448.
Kim, W., Kim, H., Citrome, L., Akiskal, H.S., Goffin, K.C., Miller, S., Holtzman, J.N., Hooshmand, F., Wang, P.W., Hill, S.J., Ketter, T.A., 2016. More inclusive bipolar mixed depression definitions by requiring fewer non-overlapping mood elevation symptoms. Acta Psychiatr. Scand. 1–10.
Koukopoulos, A., Sani, G., 2014. DSM-5 criteria for depression with mixed features: a farewell to mixed depression. Acta Psychiatr. Scand. 129, 4–16.
Koukopoulos, A., Sani, G., Ghaemi, S.N., 2013. Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV). Br. J. Psychiatry 203, 3–5.
Kraepelin, E., 1921. Manic-depressive Insanity and Paranoia. Livingstone, ES, Edinburgh.
Malhi, G.S., Das, P., Gessler, D., Outhred, T., Fritz, K., 2015. The mixed features of DSM-5. Aust. N. Z. J. Psychiatry. 49, 842–843.
Masi, G., Toni, C., Perugi, G., Mucci, M., Millepiedi, S., Akiskal, H.S., 2001. Anxiety disorders in children and adolescents with bipolar disorder: a neglected comorbidity. Can. J. Psychiatr. 46, 797–802.
Mazza, M., Mandelli, L., Zaninotto, L., Di Nicola, M., Martinotti, G., Harnic, D., Bruschi, A., Catalano, V., Tedeschi, D., Colombo, R., Bria, P., Serretti, A., Janiri, L., 2012. Bipolar disorder: "pure" versus mixed depression over a 1-year follow-up. Int. J. Psychiatry Clin. Pract. 16, 113–120.
Mcintyre, R.S., Cucchiaro, J., Pikalov, A., Kroger, H., Loebel, A., 2015a. Lurasidone in the treatment of bipolar depression with mixed (subsyndromal hypomanic) features: Post hoc analysis of a randomized placebo-controlled trial. J. Clin. Psychiatry. 76, 398–405.
Mcintyre, R.S., Soczynska, J.K., Cha, D.S., Woldeyohannes, H.O., Dale, R.S., Alsuwaidan, M.T., Gallaugher, L.A., Mansur, R.B., Muzina, D.J., Carvalho, A., Kennedy, S.H., 2015b. The prevalence and illness characteristics of DSM-5-defined "mixed feature specifier" in adults with major depressive disorder and bipolar disorder: results from the International Mood Disorders Collaborative Project. J. Affect. Disord. 172, 259–264.
Miller, S., Suppes, T., Mintz, J., Hellemann, G., Frye, M.A., Mcelroy, S.L., Nolen, W.A., Kupka, R., Leverich, G.S., Grunze, H., Altshuler, L.L., Keck Jr., P.E., Post, R.M., 2016. Mixed depression in bipolar disorder: prevalence rate and clinical correlates during naturalistic follow-up in the Stanley Bipolar Network. Am. J. Psychiatry 173, 1015–1023.
Mineo, L., Rodolico, A., Spedicato, G.A., Aguglia, A., Bolognesi, S., Concerto, C., Cuomo, A., Goracci, A., Serafini, G., Maina, G., Fagiolini, A., Amore, M., Aguglia, E., 2022. Which mixed depression model? A comparison between DSM-5-defined mixed features and Koukopoulos' criteria. Bipolar Disord. 24, 530–538.
Olgiati, P., Serretti, A., Colombo, C., 2006. Retrospective analysis of psychomotor agitation, hypomanic symptoms, and suicidal ideation in unipolar depression. Depress. Anxiety. 23, 389–397.
Perlis, R.H., Cusin, C., Fava, M., 2014. Proposed DSM-5 mixed features are associated with greater likelihood of remission in out-patients with major depressive disorder. Psychol. Med. 44, 1361–1367.
Perugi, G., Angst, J., Azorin, J.M., Bowden, C.L., Mosolov, S., Reis, J., Vieta, E., Young, A. H., Group, B.R.-I.-M.S, 2015. Mixed features in patients with a major depressive episode: the BRIDGE-II-MIX study. J. Clin. Psychiatry. 76, e351–e358.
Sato, T., Bottlender, R., Schroter, A., Moller, H.J., 2003. Frequency of manic symptoms during a depressive episode and unipolar 'depressive mixed state' as bipolar spectrum. Acta Psychiatr. Scand. 107, 268–274.
Shansis, F.M., Reche, M., Capp, E., 2016. Evaluating response to mood stabilizers in patients with mixed depression: a study of agreement between three different mania rating scales and a depression rating scale. J. Affect. Disord. 197, 1–7.
Smith, D.J., Forty, L., Russell, E., Caesar, S., Walters, J., Cooper, C., Jones, I., Jones, L., Craddock, N., 2009. Sub-threshold manic symptoms in recurrent major depressive disorder are a marker for poor outcome. Acta Psychiatr. Scand. 119, 325–329.
Spitznagel, E., Helzer, J., 1985. A proposed solution to the base rate problem in the kappa statistic. Arch. Gen. Psychiatry 42, 725–728.
Stahl, S.M., Morrissette, D.A., Faedda, G., Fava, M., Goldberg, J.F., Keck, P.E., Lee, Y., Malhi, G., Marangoni, C., Mcelroy, S.L., Ostacher, M., Rosenblat, J.D., Sole, E., Suppes, T., Takeshima, M., Thase, M.E., Vieta, E., Young, A., Zimmerman, M.,

Mcintyre, R.S., 2017. Guidelines for the recognition and management of mixed depression. CNS Spectr. 22, 203–219.
Swann, A.C., Moeller, F.G., Steinberg, J.L., Schneider, L., Barratt, E.S., Dougherty, D.M., 2007. Manic symptoms and impulsivity during bipolar depressive episodes. Bipolar Disord. 9, 206–212.
Tohen, M., Kanba, S., Mcintyre, R., Fujikoshi, S., Katagiri, H., 2014. Efficacy of olanzapine monotherapy in the treatment of bipolar depression with mixed features. J. Affect. Disord. 164, 57–62.
Verdolini, N., Hidalgo-Mazzei, D., Murru, A., Pacchiarotti, I., Samalin, L., Young, A.H., Vieta, E., Carvalho, A.F., 2018. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines. Acta Psychiatr. Scand. 138, 196–222.
Vieta, E., Bobes, J., Ballesteros, J., Gonzalez-Pinto, A., Luque, A., Ibarra, N., Spanish Group for Psychometric, S, 2008. Validity and reliability of the Spanish versions of the Bech-Rafaelsen's mania and melancholia scales for bipolar disorders. Acta Psychiatr. Scand. 117, 207–215.
Yatham, L.N., Chakrabarty, T., Bond, D.J., Schaffer, A., Beaulieu, S., Parikh, S.V., Mcintyre, R.S., Milev, R.V., Alda, M., Vazquez, G., Ravindran, A.V., Frey, B.N., Sharma, V., Goldstein, B.I., Rej, S., O'donovan, C., Tourjman, V., Kozicky, J.M., Kauer-Sant'anna, M., Malhi, G., Suppes, T., Vieta, E., Kapczinski, F., Kanba, S., Lam, R.W., Kennedy, S.H., Calabrese, J., Berk, M., Post, R., 2021. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations. Bipolar Disord. 23, 767–788.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435.
Zimmerman, M., 2003. Integrating the assessment methods of researchers in routine clinical practice: The Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project. In: First, M. (Ed.), Standardized Evaluation in Clinical Practice. American Psychiatric Publishing, Inc., Washington, DC, pp. 29–74.
Zimmerman, M., 2017. Measures of the DSM-5 mixed-features specifier of major depressive disorder. CNS Spectr. 22, 196–202.
Zimmerman, M., Mattia, J.I., 1999. Psychiatric diagnosis in clinical practice: is comorbidity being missed? Compr. Psychiatry 40, 182–191.
Zimmerman, M., Chelminski, I., Young, D., Dalrymple, K., Martinez, J.H., 2014. A clinically useful self-report measure of the DSM-5 mixed features specifier of major depressive disorder. J. Affect. Disord. 168, 357–362.